Paper RE01

Real world observational studies and the challenges in data collection

Kavitha Devadiga, Novo Nordisk, Bangalore, India
Ramya G Y, Novo Nordisk, Bangalore, India

ABSTRACT

Clinical trials are conducted in a very controlled setup. However, to see the treatment effect in real world population Real world observational studies are conducted and the data used will be called as Real-world data (RWD). In Novo Nordisk these studies are called as Non-interventional studies (NIS) and the data will be either from primary or secondary database. Since NIS are conducted in uncontrolled setup, there are many practical challenges seen during data collection ex: data fluctuation or unstructured data. However, by taking certain measures and striking balance between data collection and management, we can utilize the Real-world data to generate further evidence by complementing the results from clinical trials.

This paper will describe the challenges seen while working with data from primary database and how addressing these challenges aid the organization to collect, process and use Real-world data in a responsible, efficient, and effective manner.

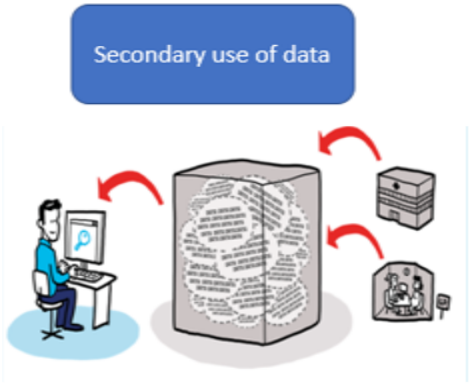
INTRODUCTION

In NIS, the data comes from the normal routine clinical practice i.e., these studies examine patients in their normal environment, taking other medication’s, eating normal diet, with acute and ongoing illness.
NIS is a type of research study in which the study product is prescribed in a way that is consistent with routine care. The decision to include the patient in the study is clearly separated from the prescription of the medicine. In addition, no additional diagnostic or monitoring procedures are performed, and epidemiological methods are used to analyze the data.

Different methods of data collection in NIS

In NIS, data comes from either primary data collection or from secondary data collection.

Data collected from Primary database is mainly used for study purpose which is obtained directly from the study patients. Here the objectives are already defined in the protocol and data will be collected to meet the requirements.



On the other hand, data from secondary data collection comes from an existing data that has been gathered previously and used for a purpose other than the study purpose. Based on the available data, objectives are defined in this setup. ex: data obtained from medical records or databases for optimization of clinical trial design etc.

Characteristics of RCT and RWE studies:

RCT (Randomized Clinical Trial)

- Strict inclusion and exclusion criteria and hence homogeneous population
- Standardized treatment
- Low risk of bias
- Better adherence and persistency to the allocated treatment
- Treatment efficacy

RWE (Real World Evidence)

- Few inclusion and exclusion criteria and hence heterogeneous population
- Routine clinical care
- High risk of bias (but depends)
- Adherence and persistency are less to the allocated treatment.
- Treatment effectiveness

Challenges in data collection and handling

Due to the pragmatic nature of the NIS studies, we can expect a lot of challenges in data collection. This paper explains few of the challenges that is seen while working on data from NIS studies based on primary database, where the study aims to complement the results generated from clinical trials.

Data collection challenges discussed in this paper pertain to:

- Informed consent visit
- Late identified screen failures
- Long in-study duration
- Intermediate visits

Informed consent visit

Informed consent means getting consent from the participant before any medical care is given to them before the study procedures. The following two scenarios illustrate the challenges seen when informed consent is obtained either before or after the V1 visit of the study, and how this issue can be addressed to prevent loss of collected data.

Scenario 1:

- V1 visit is the “Informed consent and treatment initiation visit V1”
- Informed Consent (IC) can be signed any day prior to the visit or on the day of the “Informed Consent and Treatment Initiation visit (V1)” provided that the patient has received verbal and written information and has had sufficient time to consider his/her participation.

We will investigate what happens when the reference start date for the in-study observation period is the date of the “Informed Consent and Treatment Initiation Visit V1” and patient signs IC prior to study visit V1 with an example.

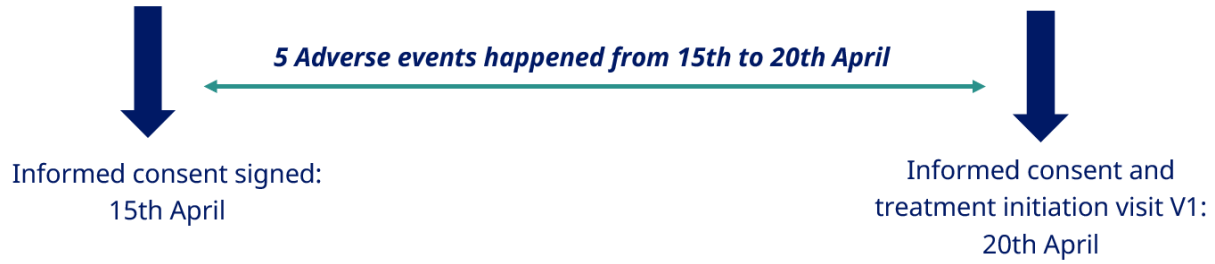


Fig A

In the example as shown in Fig A, we tend to lose 5 adverse events happening during the in-study observation period when we select reference start date as 20th April which is the "Informed consent and treatment initiation visit V1" for the study. So, this scenario directs to use 15th April which is IC date as the reference start date for in-study period to prevent the risk of losing in-study period data.

Scenario 2:
IC obtained Orally at V1 visit which is "Informed consent and treatment initiation visit V1" and signed later with different date from V1 visit for couple of patients.

If the informed consent is signed after the V1 visit, what happens when we have "Baseline measurements collected within 90 days from "V1 visit" for some parameters in the study.

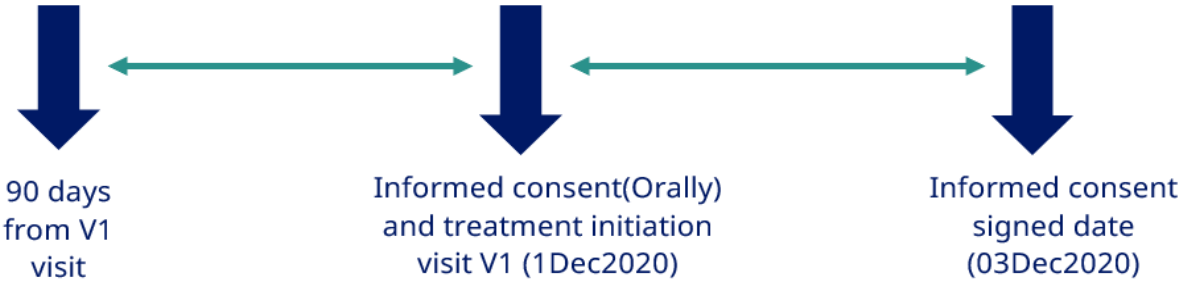


Fig B

As seen in above Fig B, if the calculated days comes to 90 days for baseline data starting from 1 Dec2020, we tend to lose baseline data if "Inform consent date" is considered as reference start date for baseline measurements. So, this scenario directs to use the V1 visit date i.e., "Inform consent and treatment initiation visit V1" 1 Dec 2020 as reference start date.

Considering the above challenges on IC date collection in NIS, it is appropriate to consider the minimum of "V1 visit date" and "Informed consent date" as the reference start date.

Reference date = Minimum (V1 visit date, Informed consent date)

Late identified Screen failures

NIS studies are designed to involve a larger and more diverse population, and therefore do not adhere to strict inclusion/exclusion (IE) criteria. This approach also improves the generalizability of study results. However, due to the less restrictive criteria, some

patients may also enter the study without meeting the IE criteria and may be identified later in the study as "Screen failures", and thus be excluded from the analysis.

Late-identified screen failures can pose challenges in meeting the required statistical power for the study and may increase the risk of unintended effects of the intervention, as well as safety risks for the patients.

Scenario: The study requires patients to be naive to certain medications as one of IE criteria and there may be situations where patients enter the study despite not meeting these criteria and complete the study.

To address this challenge at the beginning, medical specialists were consulted to conduct early surveillance of the inclusion/exclusion criteria, to mitigate the rate of late identified screen failures where the medication codes from the prior medication can be provided to them for review, so that any patients who do not meet the IE criteria can be excluded at the beginning of the study rather than waiting to be excluded at a later stage.

Early surveillance by medical specialist

Long in-study duration

Scenario: Due to pragmatic nature of the NIS sometimes the sites collect End of study (EOS) data for early enrolled patients until Last patient last visit (LPLV) of the later enrolled patient. This will lead to long in-study duration for a patient in a study thereby presenting challenge that study duration is not as per the protocol.

The challenge of retaining the protocol study duration and to prevent loss of collected data at EOS, below measures were followed.

- Defining window for the End of study visit instead of keeping it fixed visit there by allowing flexibility for attending end of study visit. In Fig C, below EOS has window ‘Week 36-46’ instead of only being as ‘Week 36’.
- Protocol clearly stating that duration of the study should be “X weeks considering individual patients” instead of “Duration should be X for the study” where the word “individual” emphasizes that duration should be taken care for individual patients.

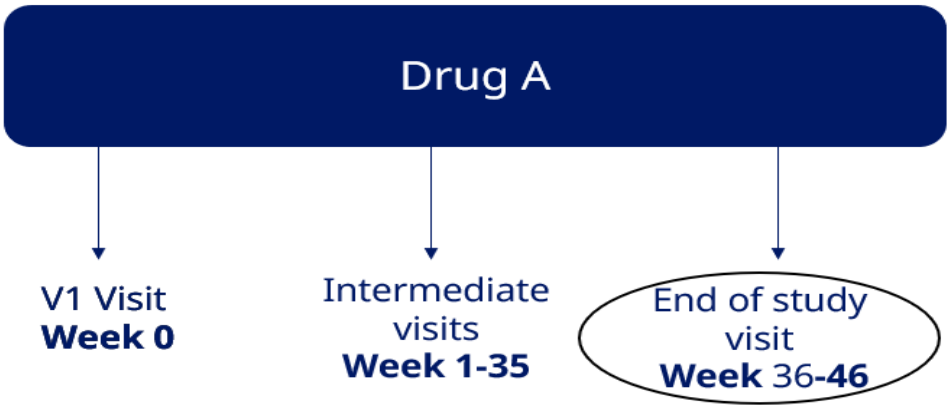


Fig C

Intermediate Visits

Intermediate visits are visits that occur between the baseline and final visits, and they can be challenging in NIS for several reasons. One reason is that they are not fixed visits in most NIS to adapt for routine clinical practice. Because of this the data may not be collected at the same timepoint for all patients and they can come to these visits any number of times as seen in Fig D below where intermediate visits are captured as V2.X where X can be any number of visits between '1-33' weeks. Because of this we see in summary table we display only fixed visits, and it also impacts on completeness of data.

	Inform Consent and treatment initiation visit	Intermediate visits according to local clinical practice	End of study visit
Visit number	V1	V2.X	V3
Time if visit (weeks[1])	0	1-33	34-44

Fig D

While there may be different methods available, but MMRM (Mixed-Effects Model Repeated Measures) is one approach used by statisticians to account for the missing data and show robustness of the results.

Key features of using MMRM model:

- MMRM is applicable where repeated measurements are collected at unscheduled timepoints.
- This model uses maximum data and calculates the estimate.
- Estimate is calculated in MMRM based on ADY and not based on visit.

[1] Weeks mentioned in Fig C and D are for presentation purpose only. This can vary depending on the study.

CONCLUSION

Overall, data collection challenges are a common and significant issue in NIS studies, but they can be addressed through careful planning and effective collaboration, we can generate more reliable and meaningful insights into the safety and effectiveness of medical interventions in real-world practice.

Disclaimer: The views and opinions expressed in this presentation belong solely to the presenter and do not necessarily reflect those of the presenter's employer, organization, committee, or any other group or individual. The purpose of this presentation is to highlight the data collection challenges encountered while working with primary databases in Non-interventional studies. No data or confidential information belonging to Novo Nordisk has been utilized in this presentation.

CONTACT INFORMATION

Your comments and questions are valued and encouraged.
Contact the author at:

Kavitha Devadiga
Novo Nordisk Service Centre India Private Ltd,
Mind Comp Tech Park, 4th Floor, EPIP Area,
Whitefield Bangalore – 560087
India Work phone: +91-6366940179
Email: kvdg@novonordisk.com
web: www.novonordisk.com

Ramya G Y
Novo Nordisk Service Centre India Private Ltd,
Mind Comp Tech Park, 4th Floor, EPIP Area,
Whitefield Bangalore – 560087
India Work phone: +91-8951747891
Email: ragy@novonordisk.com
web: www.novonordisk.com